

University of Groningen

Viability Criteria for Functional Assessment of Donor Livers During Normothermic Machine Perfusion

van Leeuwen, Otto B.; de Meijer, Vincent E.; Porte, Robert J.

Published in:
Liver Transplantation

DOI:
[10.1002/lt.25330](https://doi.org/10.1002/lt.25330)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Final author's version (accepted by publisher, after peer review)

Publication date:
2018

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

van Leeuwen, O. B., de Meijer, V. E., & Porte, R. J. (2018). Viability Criteria for Functional Assessment of Donor Livers During Normothermic Machine Perfusion. *Liver Transplantation*, 24(10), 1333-1335. <https://doi.org/10.1002/lt.25330>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Viability criteria for functional assessment of donor livers during normothermic machine perfusion

Otto B. van Leeuwen¹, Vincent E. de Meijer¹, Robert J. Porte¹

¹Department of Surgery, Section of HPB Surgery & Liver Transplantation, University of Groningen, University Medical Center Groningen, Netherlands

Corresponding author: Robert J. Porte, MD, PhD
HPB Surgery and Liver Transplantation
Department of Surgery
University Medical Center Groningen
P.O. Box 30.001
9700 RB Groningen
The Netherlands.
Tel.: +31503612896 / Fax: +31 50 361 1745
Email address: r.j.porte@umcg.nl

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/lt.25330

This article is protected by copyright. All rights reserved.

Conflict of interest: none

Financial disclosure: none

Persisting donor organ shortage has led to an increased utilization of suboptimal donor livers for transplantation. Transplantation of these extended-criteria donor (ECD) livers, however, is associated with high rates of complications, including early allograft dysfunction (EAD) and primary nonfunction (PNF). As a result, a large number of ECD livers are discarded. The decision to accept or decline an ECD liver for transplantation is largely based on empiric and rather subjective criteria available at the time of donor organ offer, but it may not reflect the actual condition of an organ after several hours of static cold storage (SCS). Ex situ machine perfusion is increasingly studied as a method to resuscitate and functionally assess donor organs shortly before transplantation. When performed at 37°C, ex situ normothermic machine perfusion (NMP) enables a metabolic assessment of high-risk liver grafts. However, there is currently no consensus on the criteria that can be used during NMP to select liver grafts that can be transplanted safely, despite initial decline based on an estimated too high of a risk for EAD/PNF.

In this issue, Mergental et al. report an interesting study in which they aimed to identify criteria that can be used during NMP to predict PNF of high-risk donor livers.¹ A total of 12 discarded human donor livers underwent NMP using a perfusion solution based on packed red blood cells for up to 6 hours after a period of SCS. Perfusate blood gas profiles, bile production, and vascular flow characteristics were examined to identify parameters that are associated with poor liver function and a high degree of injury on histology of liver biopsies. Initially, the authors identified lactate clearance as a marker for graft viability. The authors observed 2 distinct groups: a group of 6 organs with a sharp decrease in lactate levels, whereas the other 6 showed “fluctuations and rises” of the lactate levels in the perfusion solution.

After this observation, further analyses were performed by comparing these lactate clearing and nonlactate clearing groups. Secondly, the authors noted less hepatocellular injury on histology, higher hepatic ATP levels, more stable perfusate pH, and higher bile production in the lactate clearing group compared with the nonlactate clearing group. These findings supported their use of lactate as an indicator of hepatocellular function and corroborates previous results from other groups.^{2,3} Bile production, however, was observed in only 4 of the 6 livers in the lactate clearing group versus 1 out of 6 livers in the nonlactate clearing group. The authors conclude that measurable bile production can be used as a marker of good liver function, but absence of bile production does not necessarily imply poor function. Similar observations have been made by transplant groups from Cambridge and Cleveland.^{2,3} In our experience, we have noted that very low or absent bile flow can sometimes be explained by a technical issue. For example, the tip of a biliary catheter can be stuck against the bile duct wall obstructing its lumen and precluding bile flow. In addition, we have noted that bile flow through a biliary drain is dependent on the size of the drain. If the diameter of the drain is too large, bile flow may not commence easily, especially as the drain often makes an uprising loop at the rim of the reservoir (Fig. 1B and 1C in the current paper). The use of a small feeding tube catheter (8 French) with an open tip and side holes may minimize the risk of these technical issues in measuring bile production. A small size catheter provides a capillary force, facilitating bile flow. These potential issues should be considered when livers seem to produce minimal or no bile despite biochemical evidence of good functional recovery, such as a decreasing lactate level.

Collection of bile produced during NMP is important as it may aid in the assessment of bile duct viability during NMP.⁴ This is a topic not covered in the current study by Mergental et al., but it is clinically very relevant, especially in the assessment of high-risk livers donated after circulatory death (DCD). DCD liver grafts not only have an increased risk of hepatocellular dysfunction that may lead to EAD or PNF, but they are also prone to cholangiopathy due to cholangiocellular injury.⁵ Experimental and preclinical studies have

indicated that biliary pH, bicarbonate and lactate dehydrogenase during NMP may reflect biliary viability.⁴ Cholangiocytes (biliary epithelial cells) actively modify bile composition by secretion of bicarbonate and resorption of glucose, resulting in an alkalotic pH and low glucose level in bile at the level of the common bile duct. Observations made by the Cambridge group during clinical application of NMP recently supported the potential value of biliary pH in the assessment of biliary viability (and thus the risk of posttransplant cholangiopathy) during NMP.² However, more research will be needed to establish the diagnostic accuracy of bile composition in assessing biliary viability. Identification and validation of biomarkers and criteria of bile duct viability during NMP would be an important step forward in the wider utilization of DCD liver grafts.

Interestingly, Mergental et al. noted an increase in injury of the intrahepatic small bile ducts during NMP in all but 1 of the livers in the nonlactate clearing group and in 2 of the 6 in the lactate clearing group. Altogether, around 50% of the livers suffered an increase in biliary injury during NMP. Unfortunately, histological data on the large intrahepatic and or extrahepatic bile ducts were not available. Typically, these larger bile ducts are at risk of ischemia-reperfusion injury, resulting in posttransplant cholangiopathy.⁵ Although NMP may mitigate ischemia-reperfusion injury due to the absence of leukocytes and platelets in the perfusion fluid, injury due to the formation of radical oxygen species (ROS) may still occur. In fact, the first clinical studies of liver NMP have not shown a reduction in the incidence of biliary complications after transplantation compared with SCS.^{2,6} To improve results, preceding NMP by oxygenated hypothermic machine perfusion (HMP) may be more effective as the latter has been shown to resuscitate mitochondria, reduce postreperfusion ROS production and inflammation, and mitigate reperfusion injury of the bile ducts.⁷ In accordance with this, 2 preclinical studies using discarded human donor livers have recently shown that a short period of HMP prior to NMP improves metabolic recovery and attenuates oxidative stress and tissue inflammation.^{8,9} Therefore, it may be important to sequentially apply HMP and NMP, especially when NMP is used to assess the transplantability of high-

risk DCD livers, which in addition to the risk of EAD and PNF, have a high risk of developing biliary complications after transplantation.

Liver viability testing remains a highly difficult research field as the translation to clinical application must be performed with exceptional care. Based on the principle of *primum non nocere*, patient safety has to be the main concern. This has forced clinical research groups to remain on the safe side when it comes to transplantation of initially declined livers after a positive viability judgement by NMP. On the other hand, this is hampering the identification of clinically relevant cutoff values of viability criteria. With increasing experience, however, it can be expected that centers will start pushing the boundaries by stretching the acceptance criteria. As long as this process is carefully monitored and outcome data are published in a standardized fashion,¹⁰ we will collectively learn from this and be able to effectively and safely utilize the potential benefits of ex situ machine perfusion in increasing the number of suitable organs for transplantation.

References

1. Mergental H, Stephenson B, Laing RW, Kirkham A, Neil D, Wallace L et al. Development of clinical criteria for functional assessment to predict primary non-function of high-risk livers using normothermic machine perfusion. Liver Transpl. 2018
2. Watson CJE, Kosmoliaptsis V, Pley C, Randle L, Fear C, Crick K et al. Observations on the ex situ perfusion of livers for transplantation. Am J Transplant. 2018;18:2005-2020
3. Liu Q, Nassar A, Buccini L, Iuppa G, Soliman B, Pezzati D, et al. Lipid metabolism and functional assessment of discarded human livers with steatosis undergoing 24 hours normothermic machine perfusion. Liver Transpl. 2018 Feb;24:233-245

- Accepted Article
4. Weeder PD, van Rijn R, Porte RJ. Machine perfusion in liver transplantation as a tool to prevent non-anastomotic biliary strictures: Rationale, current evidence and future directions. *J Hepatol.* 2015;63:265-275
 5. de Vries Y, von Meijenfildt FA, Porte RJ. Post-transplant cholangiopathy: Classification, pathogenesis, and preventive strategies. *Biochim Biophys Acta.* 2018;1864:1507-1515
 6. Nasralla D, Coussios CC, Mergental H, Akhtar MZ, Butler AJ, Ceresa CDL et al. A randomized trial of normothermic preservation in liver transplantation. *Nature.* 2018;557:50-56.
 7. Schlegel A, Muller X, Dutkowski P. Hypothermic liver perfusion. *Curr Opin Organ Transplant.* 2017;22:563-570
 8. Westerkamp AC, Karimian N, Matton APM, Mahboub P, van Rijn R, Wiersema-Buist J, et al. Oxygenated hypothermic machine perfusion after static cold storage improves hepatobiliary function of extended criteria donor livers. *Transplantation* 2016;100:825-835
 9. Boteon YL, Laing RW, Schlegel A, Wallace L, Smith A, Attard J et al. Combined hypothermic and normothermic machine perfusion improves functional recovery of extended criteria donor livers. *Liver Transpl.* 2018. DOI: 10.1002/lt.25315
 10. Karangwa SA, Dutkowski P, Fontes P, Friend PJ, Guarrera JV, Markmann JF et al. Machine perfusion of donor livers for transplantation: a proposal for standardized nomenclature and reporting guidelines. *Am J Transplant* 2016;16:2932-2942.